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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/700,737	08/15/1996	PAUL D. PONATH	LKS95-10	4692

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EXAMINER	
SCHWADRON, RONALD B	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/700,737	PONATH ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 53-61 is/are pending in the application.

4a) Of the above claim(s) 54-58,60 and 61 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 53,59 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicant's election with traverse of the species heavy chain of SEQ ID NO:19 and light chain of SEQ ID NO:21 in the reply filed on 11/24/2004 is acknowledged. The traversal is on the ground(s) that are stated. This is not found persuasive because the species are distinct for the reasons elaborated in the previous Office Action and the searching of additional species would place a burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 57,58,60,61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/24/2004.

3. Claims 53 and 59 are under consideration. Regarding applicants comments, claim 53 is now under consideration.

4. It is noted that the prior art generally refers to "chimeric antibody" as encompassing an antibody with a variable region derived from one species and a constant region derived from a different species (eg. see references , column 3, second paragraph of Ringler et al.). It is also noted that prior art generally refers to "humanized antibody" as encompassing an antibody with a human constant region, mostly human framework regions in the variable region and substituted CDRs derived from an antibody of another species (eg. see references, column 3, second paragraph of Ringler et al.). In the instant application, the term "humanized antibody" as defined in page 12 of the specification would encompass either of the aforementioned types of antibody (entire variable region grafted or CDRs grafted).

5. The rejection of claims 1,2,4-9,13,18,23,27,28 under 35 U.S.C. 102(e) as being anticipated by Ringler et al. (US Patent 6,551,593) is withdrawn in view of the cancellation of said claims.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. The rejection of claims 1-9,11-15,18-20,23,24,27,28 under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. J. Immunol. 151 (11): 6482-6489 (Dec 1993)) and further in view of Ringler et al. (US Patent 6,551,593) and prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification) is withdrawn in view of the cancellation of said claims.

8. Claims 53 and 59 are rejected under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. J. Immunol. 151 (11): 6482-6489 (Dec 1993)) and further in view of Ringler et al. (US Patent 6,551,593) and prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification).

Queen et al. teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig. Queen et al. teach that a humanized light and heavy chain can be used to form a complete humanized Ig or antibody, having two light/heavy chain pairs, with or without partial or full-length human constant regions. Queen et al. teach that to form the humanized variable region, amino acids in the human acceptor sequence

will be replaced by the corresponding amino acids from the donor sequence if they are in a CDR (column 2, Lines 35-67). Queen et al. teach that the extent of the framework region and CDR'S have been precisely defined by Kabat et al. (column 11, Lines 38-42). Queen et al. further teach that other substitutions are required in the human framework in order for the antibody to "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen" (column 3, Lines 33-36). Queen further outlines other categories wherein amino acids in the human acceptor sequence are replaced by the corresponding amino acids from the donor sequence (column 3, lines 1-31 , in particular). Queen et al. teach that typically one of the 3-5 most homologous heavy chain variable region sequences in a representative collection of at least about 10 to 20 distinct heavy chains will be chosen as acceptor to provide the heavy chain framework, and similarly for the light chain and that the selected acceptor immunoglobulin chain will most preferably have at least about 65% homology in the framework region to the donor immunoglobulin (column 13, Lines 32-40). The 21/28'CL and GM6076'CL antibody sequences were known in the art. Queen et al. teach humanized antibodies having affinity for adhesion molecules such as fibronectin and VCAM-1. Queen et al. teach humanized anti-Tac (IL-2R) (columns 45-49). Queen et al. teach that humanized antibodies have at least three potential advantages over mouse antibodies for use in human therapy: (1) because the effector portion is human, they interact better with other parts of the human immune system, (2) they are less immunogenic, (3) they have a half-life more similar to naturally occurring human antibodies allowing smaller and less frequent doses to be given (column 16, lines 6-26). Queen et al. teach that humanized Igs can be more economically produced (column 68, Lines 12-14). Queen et al. teach compositions containing said antibody. Queen et al. do not teach the claimed humanized Act-1. Lazarovits et al. teach Act-I and that the antigen recognized by Act-I is $\alpha 4\beta 7$, the receptor for fibronectin and VCAM-1. Lazarovits et al. teach that data on T cells binding to synovium indicate that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of rheumatoid arthritis (page 6487, last paragraph). Ringler et al. teach Act-1 hybridoma which would have been used to produce the nucleic acids encoding the variable regions of Act-1 wherein said sequences would have been used to produce the claimed humanized antibody. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the

claimed invention by humanizing the Act-1 antibody as per the humanized antibodies taught by Queen et al. One of ordinary skill in the art would have been motivated to do so because Queen et al. teach their methodology can used to produce humanized antibody based on any known murine antibody and the advantages of humanized antibodies over there murine counterparts. In addition, Queen et al. disclose that humanized antibodies would be useful for therapeutic treatments, and diagnostic assays, and for purifying ligand, whilst Lazarovits et al. disclose the potential therapeutic and diagnostic value of the Act-1 antibody. The Ringler et al. reference has been added as teaching a source of the ACT-1 hybridoma. It is noted that Ringler et al. is an issued US Patent wherein the ACT-1 antibody is recited in the claims wherein the method was enabled for the use of said antibody via a publicly accessible deposit of said antibody (see column 3, last paragraph).

Regarding applicants comments about In re Deuel, the following comments are made. In re Deuel deals with issues related to the degeneracy of the nucleotides encoding for a particular amino acid sequence and the effect that this has on obtaining a particular DNA clone based on amino acid sequence data. The instant claims are not drawn to nucleic acid molecules. The cited prior art teaches molecules that are structurally similar to the claimed molecule (eg. humanized antibodies). Furthermore, even with regards to the circumstances surrounding obviousness of DNA based on knowledge of an amino acid sequence, Ex parte Goldgaber 41 USPQ2d 1173 indicates that regarding the issue of whether a method for isolating a DNA molecule makes said molecule obvious, that each case needs to be evaluated on a case by case basis depending on the particular facts in said application. Regarding the putative unexpected results disclosed in the specification, the unexpected results disclosed in the specification are not commensurate with the scope of the claimed invention. Pritsch et al. disclose that the constant domain of antibody has an effect on the binding affinity of the antibody (see abstract and discussion). Thus, any unexpected result disclosed in the specification would be related to the entire intact humanized antibody (wherein said antibody has the variable and constant region disclosed in the specification). However, the claims under consideration either do not specify the constant region of the humanized antibody or encompass only the variable region of the antibody. Therefore, the putative unexpected results disclosed in the specification are not commensurate

with the scope of the claimed invention because they require a particular constant region not recited in the claimed invention.

9. The rejection of claims 1-9,11-15,18-20,23,24,27,28 are rejected under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. J. Immunol. 151 (11): 6482-6489 (Dec 1993)) and further in view prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification) as evidenced by Tiisala et al. or Mawhorter et al. or Yuan et al. or Schulz et al. or Nieto et al. is withdrawn in view of the cancellation of said claims.

10. Claims 53 and 59 are rejected under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. J. Immunol. 151 (11): 6482-6489 (Dec 1993)) and further in view prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification) as evidenced by Tiisala et al. or Mawhorter et al. or Yuan et al. or Schulz et al. or Nieto et al.

Queen et al. teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig. Queen et al. teach that a humanized light and heavy chain can be used to form a complete humanized Ig or antibody, having two light/heavy chain pairs, with or without partial or full-length human constant regions. Queen et al. teach that to form the humanized variable region, amino acids in the human acceptor sequence will be replaced by the corresponding amino acids from the donor sequence if they are in a CDR (column 2, Lines 35-67, in particular). Queen et al. teach that the extent of the framework region and CDR'S have been precisely defined by Kabat et al. (Column 11, Lines 38-42, in particular). Queen et al. further teach that other substitutions are required in the human framework in order for the antibody to "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen" (column 3, Lines 33-36). Queen further outlines other categories wherein amino acids in the human acceptor sequence are replaced by the corresponding amino acids from the donor sequence (column 3, lines 1-31 , in particular). Queen et al. teach that typically one of the 3-5 most homologous heavy

chain variable region sequences in a representative collection of at least about 10 to 20 distinct heavy chains will be chosen as acceptor to provide the heavy chain framework, and similarly for the light chain and that the selected acceptor immunoglobulin chain will most preferably have at least about 65% homology in the framework region to the donor immunoglobulin (column 13, Lines 32-40). The 21/28'CL and GM6076'CL antibody sequences were known in the art. Queen et al. teach humanized antibodies having affinity for adhesion molecules such as fibronectin and VCAM-1. Queen et al. teach humanized anti-Tac (IL-2R) (columns 45-49). Queen et al. teach that humanized antibodies have at least three potential advantages over mouse antibodies for use in human therapy: (1) because the effector portion is human, they interact better with other parts of the human immune system, (2) they are less immunogenic, (3) they have a half-life more similar to naturally occurring human antibodies allowing smaller and less frequent doses to be given (column 16, Lines 6-26). Queen et al. teach that humanized Igs can be more economically produced (column 68, Lines 12-14). Queen et al. teach compositions containing said antibody. Queen et al. do not teach humanized Act-1 recited in the claims. Lazarovits et al. teach Act-I and that the antigen recognized by Act-I is $\alpha 4\beta 7$, the receptor for fibronectin and VCAM-1. Lazarovits et al. teach that data on T cells binding to synovium indicate that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of rheumatoid arthritis (page 6487, last paragraph). Lazarovits et al. teach Act-I hybridoma which would have been used as
a source of nucleic acids encoding the Act-1 heavy and light chain variable regions. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by humanizing the Act-1 antibody as per the humanized antibodies taught by Queen et al. One of ordinary skill in the art would have been motivated to do so because Queen et al. teach their methodology can used to produce humanized antibody based on any known murine antibody and the advantages of humanized antibodies over there murine counterparts. In addition, Queen et al. disclose that humanized antibodies would be useful for therapeutic treatments, and diagnostic assays, and for purifying ligand, whilst Lazarovits et al. disclose the potential therapeutic and diagnostic value of the Act-1 antibody. The cited evidentiary references disclose the public availability of the Act-1 hybridoma.

Applicants arguments are addressed in paragraph 8 of this Office Action.

11. The rejection of claims 1-9,11-15,18-20,23,24,27,28 under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. (1993), Springer et al. (Leucocyte Typing V), Petell et al., Huston et al. (US Patent 5,258,498) and further in view prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification) is withdrawn in view of the cancellation of said claims.

12. Claims 53 and 59 are rejected under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. (1993), Springer et al. (Leucocyte Typing V), Petell et al., Huston et al. (US Patent 5,258,498) and further in view prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification)

Queen et al. teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig. Queen et al. teach that a humanized light and heavy chain can be used to form a complete humanized Ig or antibody, having two light/heavy chain pairs, with or without partial or full-length human constant regions. Queen et al. teach that to form the humanized variable region, amino acids in the human acceptor sequence will be replaced by the corresponding amino acids from the donor sequence if they are in a CDR (column 2, Lines 35-67). Queen et al. teach that the extent of the framework region and CDR'S have been precisely defined by Kabat et al. (Column 11, Lines 38-42, in particular). Queen et al. further teach that other substitutions are required in the human framework in order for the antibody to "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen" (column 3, Lines 33-36). Queen further outlines other categories wherein amino acids in the human acceptor sequence are replaced by the corresponding amino acids from the donor sequence (column 3, lines 1-31). Queen et al. teach that typically one of the 3-5 most homologous heavy chain variable region sequences in a representative collection of at least about 10 to 20 distinct heavy chains will be chosen

as acceptor to provide the heavy chain framework, and similarly for the light chain and that the selected acceptor immunoglobulin chain will most preferably have at least about 65% homology in the framework region to the donor immunoglobulin (column 13, Lines 32-40). The 21/28'CL and GM6076'CL antibody sequences were known in the art. Queen et al. teach humanized antibodies having affinity for adhesion molecules such as fibronectin and VCAM-1. Queen et al. teach humanized anti-Tac (IL-2R) (columns 45-49). Queen et al. teach that humanized antibodies have at least three potential advantages over mouse antibodies for use in human therapy: (1) because the effector portion is human, they interact better with other parts of the human immune system, (2) they are less immunogenic, (3) they have a half-life more similar to naturally occurring human antibodies allowing smaller and less frequent doses to be given (column 16, Lines 6-26). Queen et al. teach that humanized Igs can be more economically produced (column 68, Lines 12-14). Queen et al. teach compositions containing said antibody. Queen et al. do not teach the humanized Act-1 recited in the claims. Springer et al. teach the Act-1 antibody (AKA S254 (se page 1450) and the distribution of said antibody (see page 1443, first column). Petell et al. teach that the sequence of the VH and VL encoding a known antibody can be determined by amino acid sequencing analysis of said antibody (see column 6). Huston et al. also teach that the sequence of VH and VL of a known antibody can be determined by amino acid sequencing. Huston et al. teach that:

"The 5' end portion of the mRNA can be used to produce the cDNA for subsequent sequencing or the amino acid sequence of the hypervariable and flanking framework regions can be determined by amino acid sequencing of the V regions of the H and L chains. Such sequence analysis is now conducted routinely.".

Lazarovits et al. teach Act-I and that the antigen recognized by Act-I is $\alpha 4\beta 7$, the receptor for fibronectin and VCAM-1. Lazarovits et al. teach that data on T cells binding to synovium indicate that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of rheumatoid arthritis (page 6487, last paragraph). Lazarovits et al. teach Act-I hybridoma which would have been used as a source of nucleic acids encoding the Act-1 heavy and light chain variable regions. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by humanizing the Act-1 antibody as per the humanized antibodies taught by Queen et al. using amino acid sequence

information derived from sequencing the Act-1 antibody. One of ordinary skill in the art would have been motivated to do so because Queen et al. teach their methodology can used to produce humanized antibody based on any known murine antibody and the advantages of humanized antibodies over there murine counterparts. In addition, Queen et al. disclose that humanized antibodies would be useful for therapeutic treatments, and diagnostic assays, and for purifying ligand, whilst Lazarovits et al. disclose the potential therapeutic and diagnostic value of the Act-1 antibody.

Applicants comments are addressed in paragraph 8 of this Office Action.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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